Conservation Science
Translating Knowledge into Actions

Pharmaceutical drugs and other substances with pharmacological activity in the environment: a threat to biodiversity?

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Summary

Drugs of human origin are now dispersed in all ecosystems, and non-target exposed biota are likely to be impacted in the future by a large number of substances with unpredictable consequences. One of the potential effects of drugs (and other substances with pharmacological activity) is the exertion of selective pressure, favouring an artificial process of selection, in which sensitive organisms may be favoured. We bring to discussion the consequences expected from chronic environmental exposure of biota to two major classes of chemicals that are nowadays released thoroughly into the environment: stimulants and neuroendocrine drugs.

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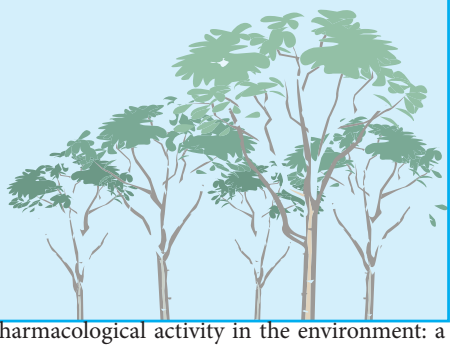

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The presence of pharmaceutical drugs and their residues in the wild is nowadays an indisputable reality. Vast is the number of substances that fall into this specific class that have already been found, identified and quantified in a multitude of environmental matrices (Neng and Nogueira 2012, Morais et al. 2013, Brambilla and Testa 2014). Not only pharmacologically active substances, but others that co-exist with drugs in commercial therapeutic formulations, form a vast group entitled pharmaceutical and personal care products (PPCPs), whose fate, effects and dispersion routes are not entirely elucidated. The number of studies showing the presence of such substances is ever increasing, a factor that should call the attention of conservation scientists for the potential consequences of such a wide dissemination. In fact, pharmaceutical substances are, contrarily to what occurs for a large number of anthropogenic compounds, biologically active, and will continue to exert their effects once they are released into the ecosystem. Considering that the majority of drugs are excreted, ending up being discarded into the aquatic environment with or without treatment, aquatic organisms are likely to be more impacted than others (Fang et al. 2012). Additional evidences point to the global dispersion phenomenon of PPCPs: from tropical areas (Montagner et al. 2013) to Polar Regions (Kallenborn et al. 2008).

Drugs are produced, prescribed and sold in order to exert an effect, both in humans and in animals. This effect may be mediated by the activation of a receptor, a process or a pathway that generally is not exclusive to the target organism (Sanderson et al. 2004, Crane et al. 2006, Kugathas and Sumpter 2011). Indeed, an increasing number of studies have shown the homology or processes that can be affected both in target and non-target organisms, exposed via environment to pharmaceutical drugs. Consequently, drugs can thus exert effects in a large number of organisms; however, these effects are not always beneficial, and can be deleterious in nature. For the majority of organisms, lack of data concerning toxicological and pharmacological responses caused by pharmaceutical drugs makes even more difficult to elaborate an accurate prediction of the global consequences. Despite the apparent lack of data concerning the effects of pharmaceutical drugs on wildlife, some studies suggest that some species appear to be more sensitive than others. Consequently, the response to drugs is, in some cases, likely to occur especially in more sensitive species. Some recent studies have also showed that plants are also potential targets for the exertion of toxicity by specific substances, such as paracetamol (Nunes et al. 2014). The effects of drugs do not occur only at the individual level, ecosystems are likely to be impacted by this type of contaminants (Ferguson et al. 2013, Proia et al. 2013, Oskarsson et al. 2014).

Despite the extremely low levels in which drugs are found in the wild (especially in the aquatic environment), this fact does not prevent them for exerting toxic effects; in fact, some substances can trigger biological effects in almost insignificant amounts. It is with no surprise that this can happen, since therapeutic agents are designed and synthesized to achieve maximum efficacy with the lowest possible dosage. A similar trend occurs in the wild, and the most affected species are those exhibiting higher responsiveness towards a specific pharmaco-therapeutic group. By being affected, and consequently vulnerable to a specific type of pharmaceutical agents, some species are in relative disadvantage in relation to others, more resistant and robust when exposed to these contaminants. The individual effects caused by pharmaceutical exposure may have consequences in the long term, and for the entire ecosystem. As shown by the work of Ginebreda et al. (2010), exposure of wild aquatic communities to common pharmaceuticals can result in the loss of biodiversity. The mechanistic explanation of this effect is still not completely elucidated, due to the large number and variety of compounds found in river water, but a linkage between drug contamination and impacts on biodiversity seems to be clear. The most striking example of biodiversity challenge caused by drugs in the wild is linked to the environmental contamination by antibiotics, and the selection of resistant bacterial strains, or the horizontal dispersal of resistances genes among distinct species of bacteria (Davison 1999). By favouring the dispersal of resistance genes, antibiotics act on bacterial populations by means of making their genomes more uniform and similar (Barkovskii et al. 2012), eroding the diversity of genetic traits among species. Additionally, several antibiotics select only resistant organisms; the work published by Kong et al. (2006) showed that the antibiotic drug oxytetracycline could decrease the diversity of soil community microorganisms.

Some of the already reported substances in the wild have modes of toxicological activity that may have profound implications in ecological terms. This is the case of neuroendocrine substances, and central nervous system stimulants, therapeutic classes that will be further discussed. Other examples come from estrogenic compounds used for birth control, antineoplastics used in cancer therapy, anti-inflammatory drugs extensively used and released into the aquatic ecosystem Kümmerer et al. 1997, Halling-Sørensen et al. 1998, Heberer 2002). In such cases, the consequences of exposure to these compounds may have repercussions far beyond the life cycle of exposed organisms. In fact, effects may involve long lasting traits, such as reproductive alterations, and cognition/learning enhancement etc. Considering that some species may be differentially sensitive towards distinct compounds, alterations caused by both drug classes may also occur in different terms: not all species will have their behaviour altered in a similar way and/or extension. This differential expression of effects may imply competitive advantages for the most sensitive or-

ganisms, altering the ecosystem balance and challenging biodiversity.

Caffeine is widely consumed by humans as a mild stimulant, and in combination with other drugs to treat migraine and pain (Sawynok et al. 1995). Additionally, it has also been used to treat apnoea consequences in prematurely born infants (Davis et al. 2010). However, its neuroactive effects are not limited to patients that use it therapeutically or to their regular consumers (coffee, its derivatives and soft drinks). Caffeine enters continuously into the aquatic environment mainly by two distinct routes: in the metabolised form after being ingested by humans and treated by sewage treatment plants; or by direct disposal from the coffee industry (Martínez Bueno et al. 2011). Caffeine was one of the first chemicals used by humans that were clearly implicated in behavioural alterations on other organisms, as shown by Castellano (1976). This stimulant was implicated in the consistent and long-lasting modification of natural vs, apprehended behaviour in rodents. In fact, caffeine can alter several processes directly related to the activity of the central nervous system of exposed organisms, such as memory processing in insects (Si et al. 2005, Mustard et al. 2012) and rodents (Angelucci et al. 1999, Abreu et al. 2011, Angelucci et al. 2002), alterations which may constitute an advantage for spatial processing and avoidance, object recognition, and learning. By increasing the cognitive and learning abilities of susceptible species, exposure to caffeine can thus trigger the development of a competitive advantage over non-susceptible organisms, which is of natural ecological implication. Due to its worldwide presence, especially in the aquatic compartment, and even in marine areas (Nödler et al. 2014, Weigel et al. 2002), it is possible to anticipate that a large number of distinct organisms can be environmentally exposed to caffeine. Consequently, the exertion of biological effects is extremely likely, despite its low levels, especially in sensitive species. It is thus not possible to exclude that caffeine may alter behavioural traits of some aquatic species, granting them an intrinsic advantage over others. This advantage may contribute for altered patterns in various features, such as increased predation, consequently altering the ecosystem functioning and ultimately, biodiversity.

Hormonal compounds, both natural and synthetic, are able to alter the reproductive behaviour and features of exposed organisms. This was recognized a long time ago, when the effects of a specific class of therapeutic substances (such as oral contraceptives, that include synthetic oestragens; eg: 17α aethinylestradiol), were observed in test organisms; since then, this specific compound has been considered a disruptive compound for aquatic organisms (Souza et al. 2013), capable of altering population structures. In fact, the importance of such substances in ecological terms and the potential ecosystem impact that may derive from exposure to such chemicals lead to their identification as priority substances requiring further studies (Runnalls et al. 2010). Other types of compounds that are not of hormonal nature and designated as neuroendocrine compounds may alter other aspects of the organism's physiology including reproductive behaviour (Waye and Trudeau 2014) and energy balance (Mennigen et al. 2010). Pharmaceuticals already shown to be capable of exerting such effects include antifungal compounds (clotrimazole and ketoconazole), antidepressants of the class of the selective serotonin reuptake inhibitors (mianserin, van der Ven, 2006; fluoxetine, Mennigen et al. 2010, 2011), furosemide and several fibrates (bezafibrate, fenofibrate and gemfibrozil; Isidori et al. 2009), and mefenamic acid (Collard et al. 2013). By compromising reproductive traits and patterns, which should be of greater significance in more sensitive species, it is possible that these substances may alter the population structure with evident effects in terms of community and ecosystem, including biodiversity.

In conclusion, it is possible to state that the majority of drugs do not pose immediate ecological risks; however, and for some specific classes of compounds, behavioural and/or reproductive effects are the most likely consequences, which may imply subtle alterations in population structures. More than being mere evolutionary trends, these future modifications that are now being documented for the first time, may be the final linkage between pharmaceutical exposure and ecological effects. More studies are now required, aiming to a more comprehensive approach towards understanding the long-term effects of pharmaceuticals exposure in populations, namely of aquatic organisms. More than establishing subindividual and individual effects (which were already demonstrated), field studies are mandatory to know the details of ecosystem impairment that may occur due to cognitive and reproductive changes elicited by drugs. To tackle the challenges to come, it will be important to prioritise specific compounds (or classes of compounds) that will require further testing (namely, under chronic, long term conditions), based on pre-existing knowledge. Considering the two above-mentioned classes (stimulants and neuroendocrine compounds), it is already possible to sustain that these might be priority chemicals, considering their long terms and irreversible effects. Broad programs of monitoring, under field and real time conditions, will also be important to address the immense possibilities of interference with biodiversity; microbial communities, for example, are more simply to follow than vertebrates. To encompass this issue, regulations on pharmaceutical commerce must include assessment of biodiversity effects as mandatory parameters.

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Biography